# The hydroboration of enamines

**Christian T. Goralski*[a] and Bakthan Singaram[b]**

[a] *CTG Consulting, LLC, 2773 North Cedaridge Drive, Midland, Michigan 48642, USA*
[b] *The Department of Chemistry and Biochemistry, University of California Santa Cruz, 1156 High Street, Santa Cruz, California 95064, USA*
*E-mail: goralskiconsult@aol.com, singaram@chemistry.ucsc.edu*

**Dedicated to Professor Keith Smith on the occasion of his 65th anniversary**

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**Abstract**

This review describes the hydroboration of enamines in chronological order covering early work to give β-amino alcohols and reduction products and then our more recent work to give β-aminoorganoboranes and their subsequent conversion into β-amino alcohols, β-aminoboronic esters and acids, and olefins. Analytical methods to determine the enantiomeric excess (ee) of the β-amino alcohols obtained from the asymmetric hydroboration of enamines are also described.

**Keywords:** Enamines, hydroboration, asymmetric hydroboration, β-amino alcohols, β-aminoboronic acids and esters

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## 1. Introduction

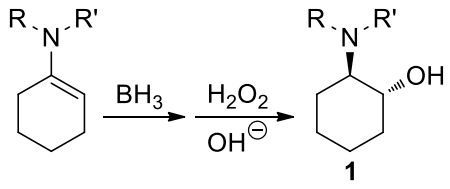
The hydroboration of enamines affords β-(dialkylamino)alkylboranes which can be converted into the corresponding β-(dialkylamino)alkylboronate esters and acids, β-(dialkylamino)alkyl alcohols, and olefins. This review describes early studies of the hydroboration of enamines, and

then covers our detailed study of enamine hydroboration and analytical methods developed to determine the enantiomeric excesses in asymmetric hydroboration of enamines.

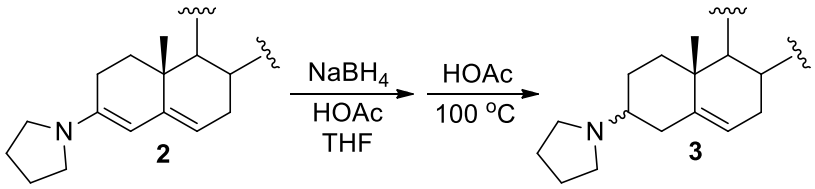
## 2. The Early Years of Enamine Hydroboration

The first report of the hydroboration of an enamine appeared in 1961, when Stork reported that the hydroboration of an unspecified cyclohexanone enamine followed by oxidative cleavage of the borane with alkaline hydrogen peroxide afforded a racemic *trans*-2-hydroxycyclohexylamine **1** (Equation 1).[1]



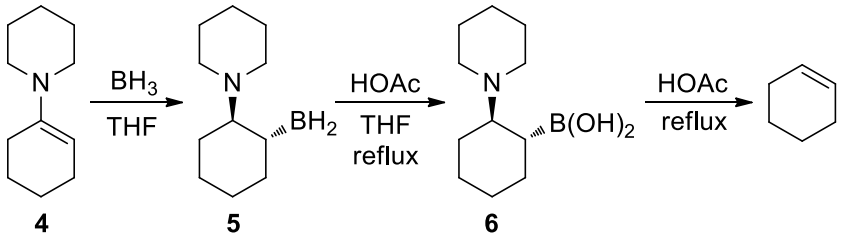

(**1**)

Two years later, Marshall and Johnson[2] reported that when the pyrrolidine dieneamine **2** was reacted with diborane in THF and the resulting solution of the borane refluxed with acetic acid, 3β-pyrrolidinocholest-5-ene (**3**) was formed in 44% yield (Equation 2).




(**2**)

In an attempt to repeat the work of Marshall and Johnson with 1-(1-piperidino)cyclohexene (**4**), Lewis and Pearce reported, in a 1964 communication[3] and a 1969 full paper,[4] the isolation of 2-(1-piperidino)cyclohexaneboronic acid (**6**) in nearly quantitative yield (Equation 3).



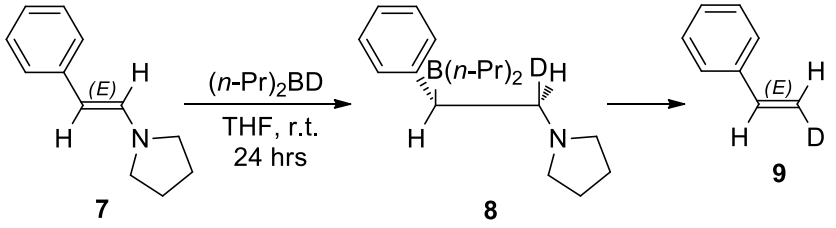

(**3**)

When compound **6** was refluxed with acetic or propionic acid in diglyme, cyclohexene was obtained. The intermediate borane **5** was unaffected when it was heated at reflux in diglyme, but was converted into cyclohexene when a carboxylic acid was added. The

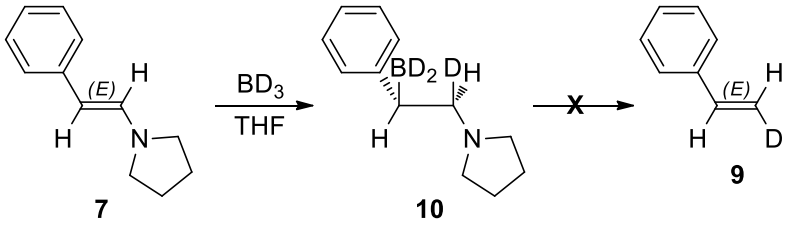
hydroboration/elimination procedure was applied to a variety of enamines of cyclic and acyclic ketones to give the corresponding alkenes in yields of greater than 85%.

In 1966, Pasto and Snyder[5] reported that deuterioboration of (*E*)-1-phenyl-2-(1-pyrrolidino)ethene (**7**) with "(*n*-Pr)$_2$BD" (40% (*n*-Pr)$_3$B, 38% (*n*-Pr)$_2$BD, 22% *n*-PrBD$_2$)[5] in THF resulted in the formation of "moderate amounts" of **8** which underwent elimination to give (*E*)-1-phenyl-2-deuteroethene (**9**) in 14% yield (Equation 4).



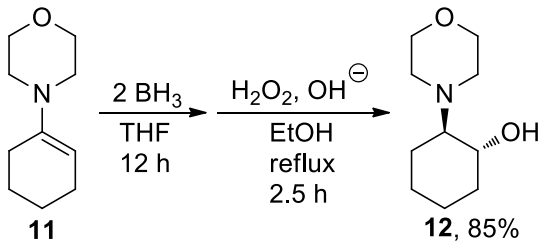

(**4**)

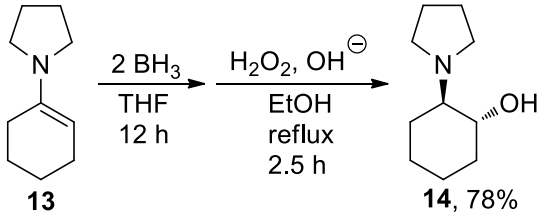
In contrast, deuterioboration of **7** with $BD_3$ in THF gave **10**, which did not undergo uncatalyzed elimination (Equation 5).




(**5**)

In 1967, Borowitz and Williams[6] reported that the hydroboration of the morpholine (**11**) or pyrrolidine (**13**) enamine of cyclohexanone with two equivalents of $BH_3$ in THF, followed by treatment with basic hydrogen peroxide, afforded the corresponding *trans*-2-(dialkylamino)-cyclohexanols in good yield (Equations 6 and 7, respectively).

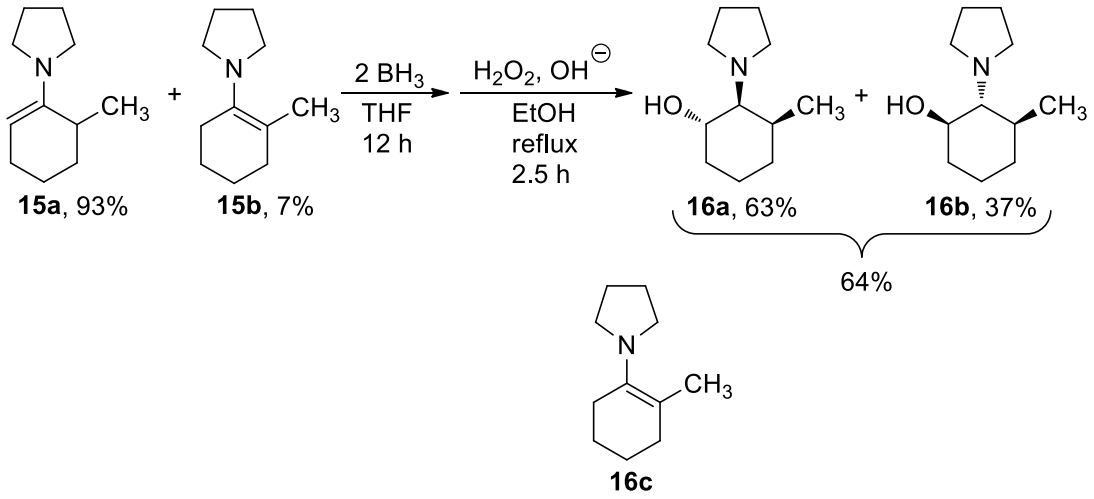



(**6**) (**7**)

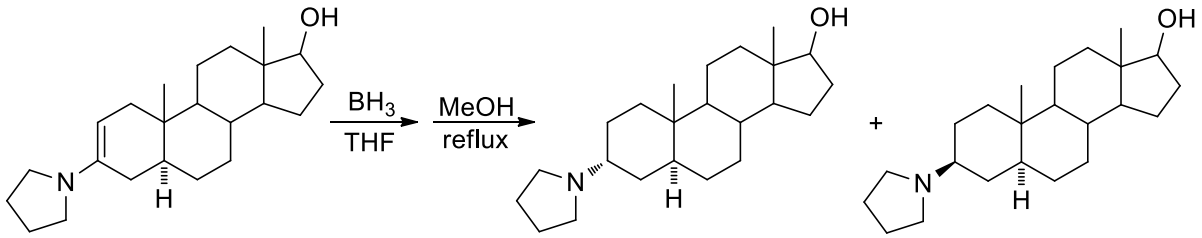
 

Similarly, hydroboration/oxidation of the pyrrolidine enamine of 2-methylcyclohexanone (**15a**, **15b**) gave a 64% yield of a 63:37 mixture of the isomeric amino alcohols **16a** and **16b**, with no detectable amount of the tertiary alcohol **16c** (Equation 8).



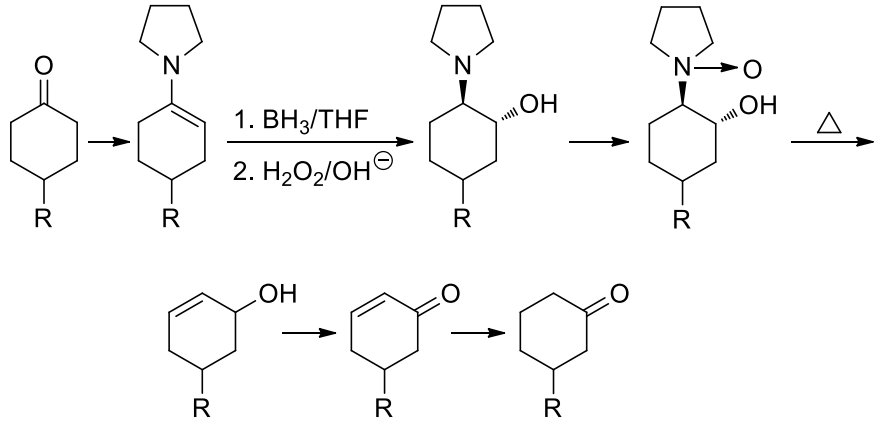

(**8**)

In 1970, Gore and Barieux[7] reported, in the first of a series of six papers, that the hydroboration of the pyrrolidine enamine of dihydrotestosterone **17** with diborane in THF followed by treatment of the intermediate organoborane with refluxing methanol afforded an 80-85% yield of an 82:18 mixture of the isomeric aminosteroids **18a** and **18b** (Equation 9).




(**9**)

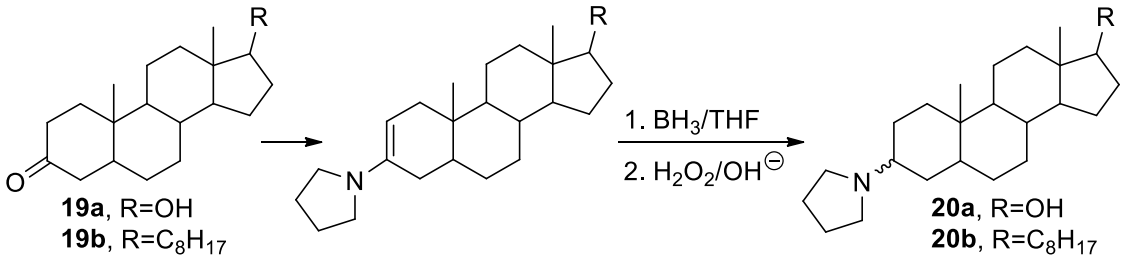
In the following year, Barieux and Gore reported a 1,2-carbonyl transposition sequence in which the hydroboration/oxidation of an enamine to the corresponding *trans*-2-aminoalcohol was a key step (Equation 10).[8-10]




(**10**)

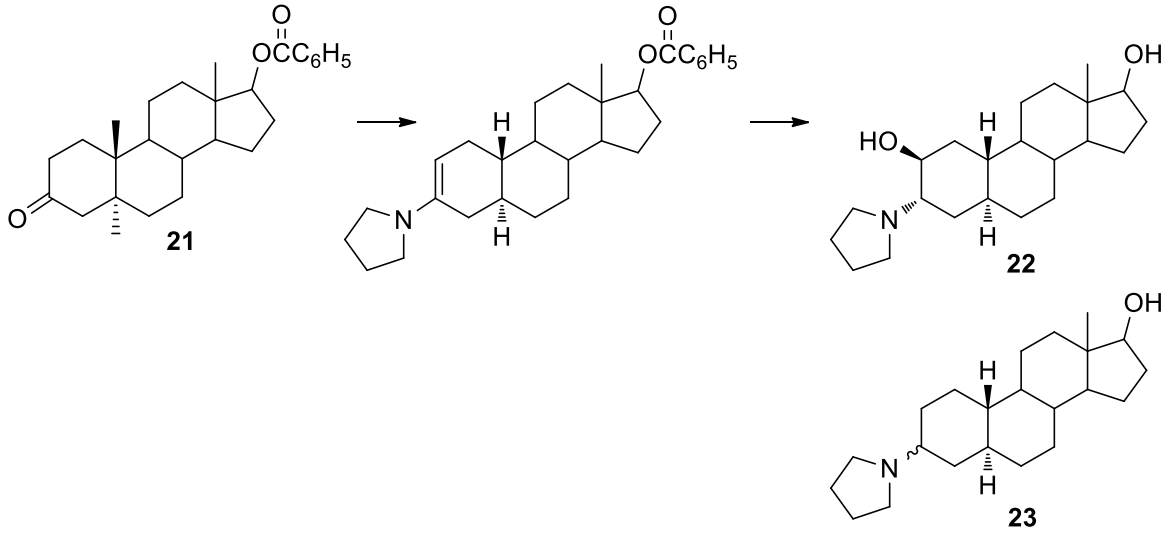
 

In 1972, Barieux and Gore reported the results of further studies on the hydroboration of enamines of 3-ketosteroids.[11,12] Hydroboration/oxidation of the enamines of 3-ketosteroids containing a 19-methyl group (**19a**, **19b**) afforded, instead of the 2-amino-alcohols, a mixture of the corresponding isomeric aminosteroids (**20a**, **20b**, Equation 11).




(**11**)

In contrast, hydroboration/oxidation of the enamine of a 3-ketosteroid containing no 19-methyl group, the pyrrolidine enamine of the benzoate of 5α-oestranol-17β-one-3 (**21**), afforded a 75% yield of an 82:18 mixture of the corresponding *trans*-amino alcohol **22** and the aminosteroid **23** (Equation 12).

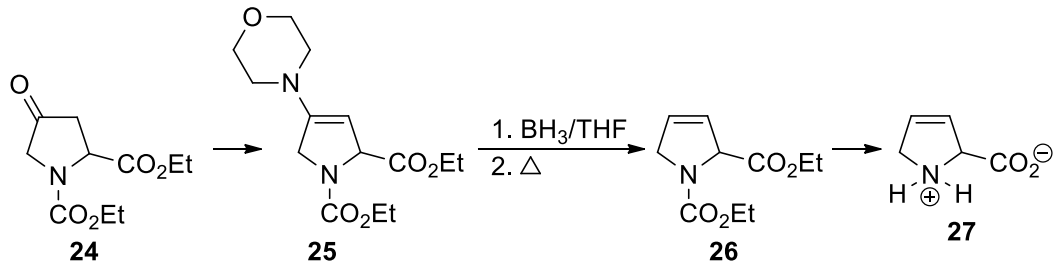



(**12**)

From this study, the authors concluded that in systems in which the amino group and the $BH_2$ group are in the *trans*-diequatorial orientation, amino alcohols are the predominant products, and in systems in which the amino group and the $BH_2$ group are in the *trans*-diaxial orientation the reduced products (aminosteroids) predominate.

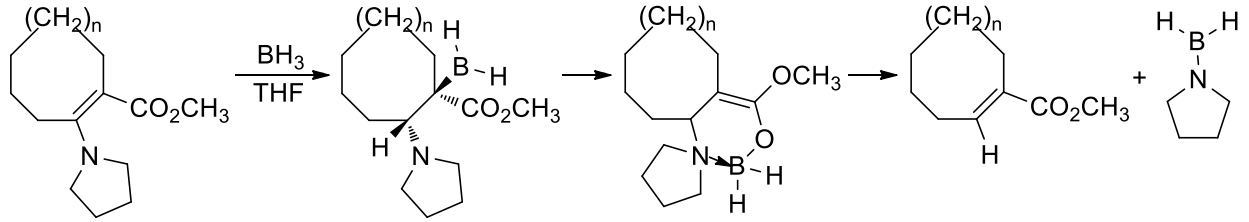
In 1973, Franck *et al*.[13] described a synthesis of dehydroproline (**27**), the key step of which was the one-pot conversion of ketone **24** to olefin **26** via hydroboration/elimination of the enamine **25** (Equation 13).



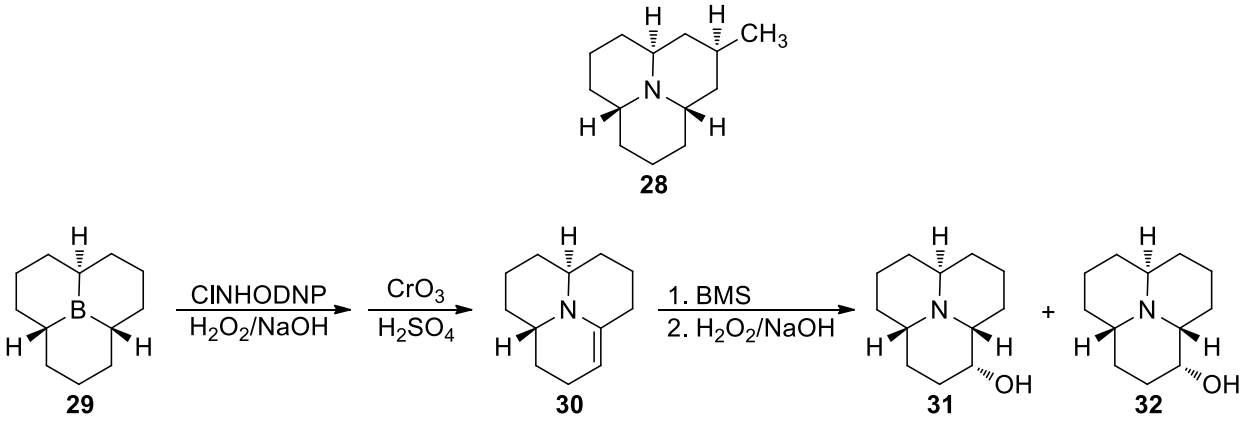

(**13**)

Three years later, Fruborg, Magnussen, and Thoren[14] reported the hydrogenolysis of a series of β-enamino methyl esters with $BH_3$ in THF to give the corresponding α,β-unsaturated esters (Equation 14).




(**14**)

In 1980, Mueller and Thompson[15] described the hydroboration of an enamine in the synthesis of the ladybug defensive agent hippodamine (**28**). Hydroboration/oxidation of the enamine **30**, prepared stereoselectively in two steps from perhydroboraphenalene (**29**), gave a 95% yield of a 3:1 mixture of the alcohols **31** and **32**, respectively (Equation 15).



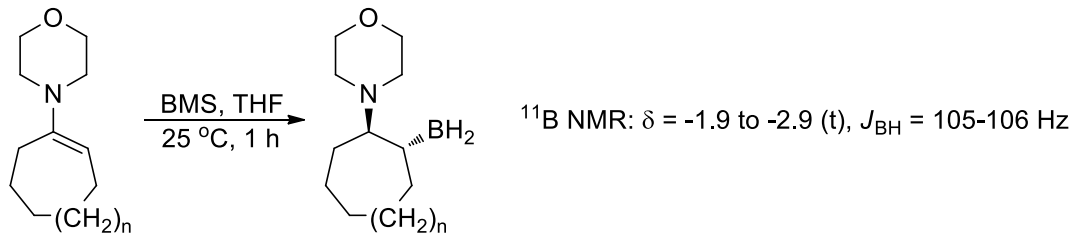

(**15**)

## 3. Investigations of the Hydroboration of Enamines by Goralski, Singaram, and Brown

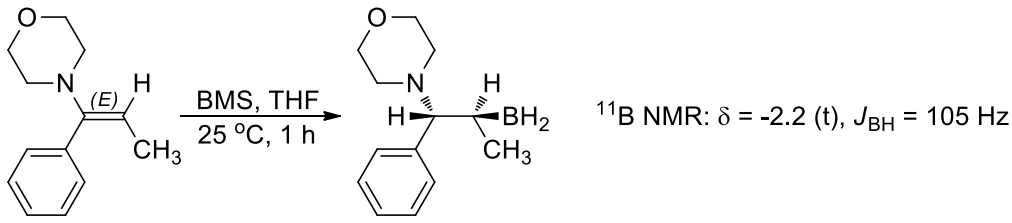
In the mid-1980s we became interested in developing the asymmetric hydroboration of enamines as a method of preparing chiral amino alcohols with high enantiomeric excesses (ee). Because the earlier studies on the hydroboration of enamines reported, in addition to 2-amino alcohols, reduction products and elimination products, we decided to re-investigate the hydroboration of a series of enamines with borane methylsulfide (BMS) in THF to determine how these different products were formed. In 1987, we published the results of our studies.[16]

The hydroboration of a series of 1-(4-morpholino)cycloalkenes with one equivalent of BMS in THF afforded the corresponding *trans*-2-(4-morpholino)cycloalkylboranes in high yield (Equation 16).[16]




(**16**)

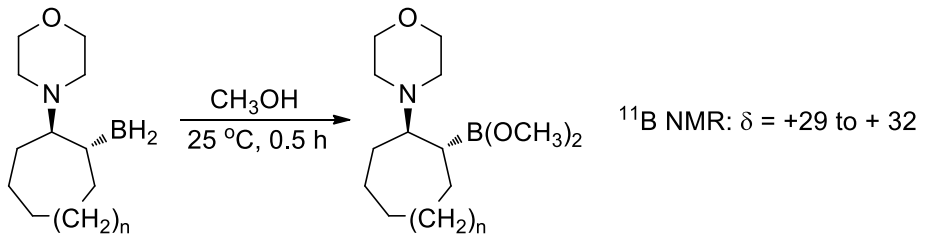
Similarly, hydroboration of (*E*)-1-(4-morpholino)-1-phenyl-1-propene (**33**) under the same conditions afforded *threo*-1-(4-morpholino)-1-phenyl-2-propylborane (**34**) in high yield (Equation 17).[16]

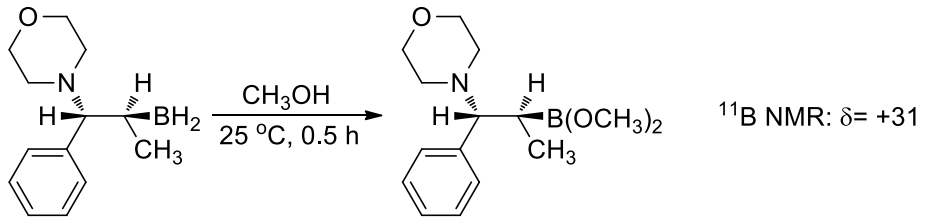



(**17**)

Treatment of these boranes with methanol afforded the corresponding dimethyl boronate esters in 73-86% yields (Equations 18 and 19).[16]

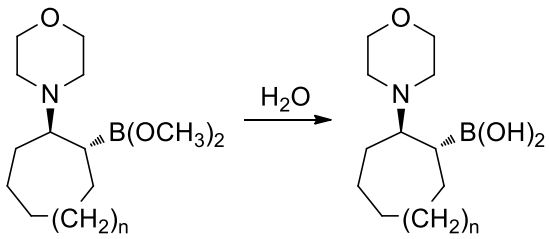
 

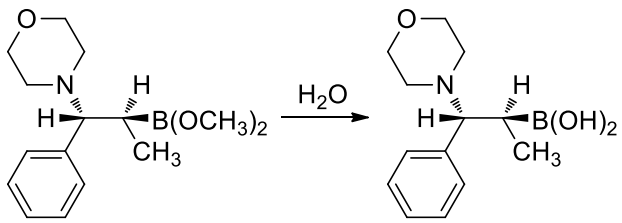



(**18**) (**19**)

The dimethyl boronate esters were readily hydrolyzed with water to give the corresponding boronic acids in 84-90% yields (Equations 20 and 21).[16]

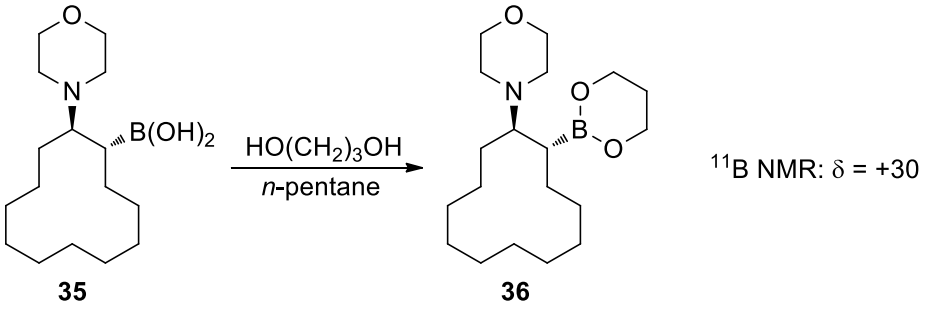



(**20**) (**21**)

Treatment of *trans*-2-(4-morpholino)cyclododecylboronic acid (**35**) with 1,3-propanediol in *n*-pentane afforded *trans*-2-(4-morpholino)cyclododecyl-1,3,2-dioxaborinane (**36**) in 86% yield (Equation 22).[16]




(**22**)

The preparation of amino alcohols from 1-(dialkylamino)cycloalkenes by hydroboration with BMS followed by methanolysis and oxidation with alkaline hydrogen peroxide was also investigated, and the results are summarized in Figure 1.[16] Similar to 1-(4-morpholino)-cyclododecene (see Figure 1), the acyclic enamine (*E*)-1-(4-morpholino)-1-phenyl-1-propene (**33**), upon hydroboration/methanolysis/oxidation, gave pure (*E*)-1-phenyl-1-propene in 50% yield and *threo*-1-(4-morpholino)-1-phenyl-2-propanol (**37**) in 35% yield (Equation 23).[16]

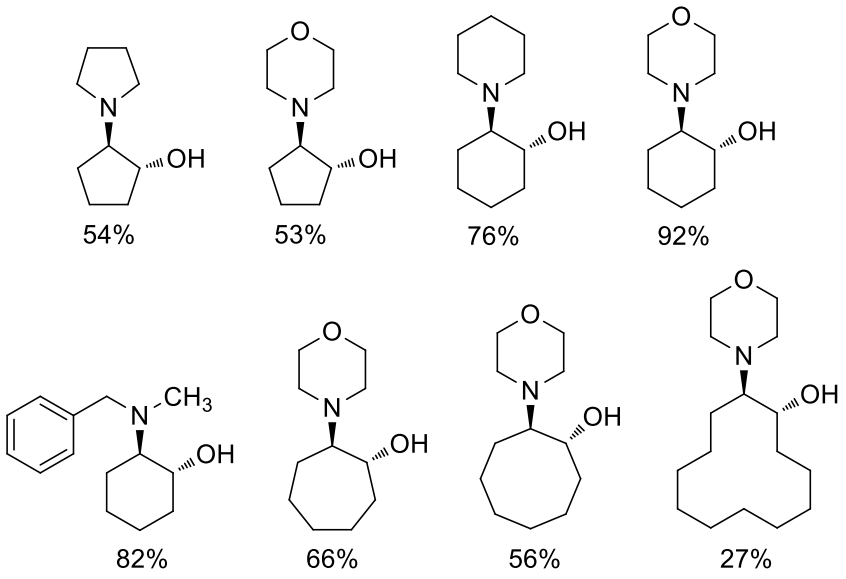
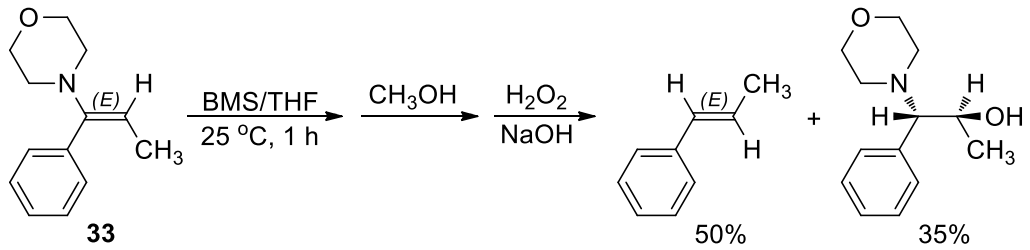



**Figure 1.** Structures of the *trans*-2-(dialkylamino)cycloalkanols prepared by the hydroboration (BMS/THF)/methanolysis/oxidation ($H_2O_2$/NaOH) of the corresponding 1-(dialkylamino)cyclo-alkenes (yields shown are of isolated and distilled materials). The major product obtained from 1-(4-morpholino)cyclododecene was *trans*-cyclododecene, which was isolated in 55% yield.

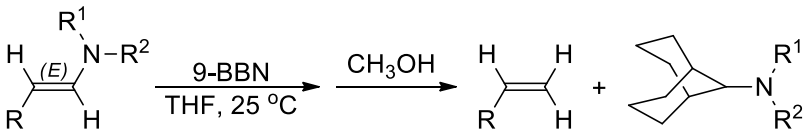



(**23**)

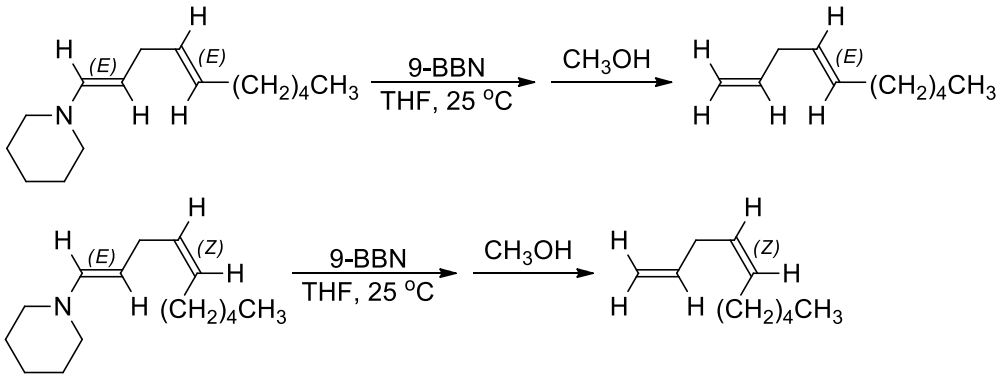
Several years later, we described the conversion of aldehydes and ketones into the corresponding (*E*)- or (*Z*)-alkenes via the hydroboration of their enamines.[17-20]

Hydroboration of aldehyde enamines by 9-BBN followed by methanolysis afforded the corresponding terminal alkenes in excellent yields (Equation 24).



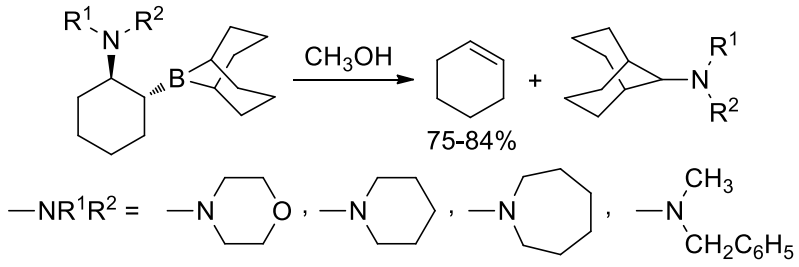

**(24)**

Hydroboration of the enamines of unsaturated aldehydes by 9-BBN followed by methanolysis afforded the corresponding dienes, demonstrating the remarkable chemoselectivity of the hydroboration reaction for the enamine double bond. Thus, (*E*)-1-(4-morpholino)-1(*E*)-4-decadiene afforded 1,4(*E*)-decadiene in 82% yield and 1-(4-morpholino)-1(*E*),4(*Z*)-decadiene afforded 1,4(*Z*)-decadiene in 89% yield (Equations 25 and 26).[19,20]




**(25)** **(26)**

Enamines from cyclic ketones, for example cyclohexanone, gave the corresponding cycloalkenes (Equation 27). The reaction was independent of the nature of the secondary amine employed.[19,20]

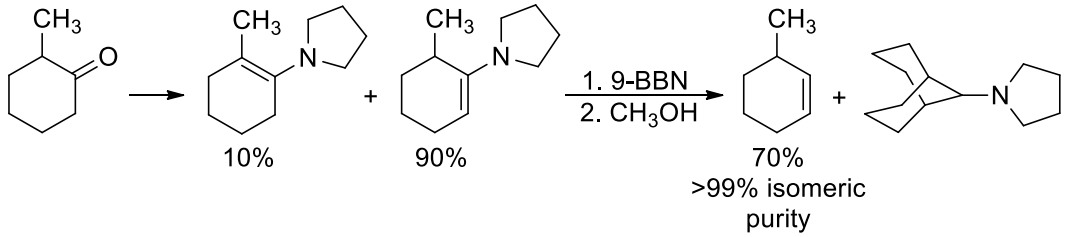



**(27)**

It was previously reported that the formation of pyrrolidine enamines of 2-alkylcycloalkanones is highly regiospecific, producing the less substituted enamine.[21] We took advantage of this fact to convert 2-alkylcyclohexanones into 3-alkylcyclohexenes

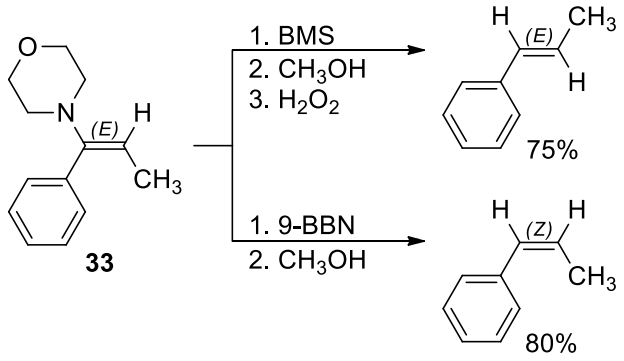
 

regiospecifically.[19,20] For example, 2-methylcyclohexanone was converted to a mixture of 90% 6-methyl-1-pyrrolidinocyclohexene and 10% 2-methyl-1-pyrrolidinocyclohexene, which was subsequently converted by hydroboration with 9-BBN followed by methanolysis to 3-methylcyclohexene (Equation 28).




(**28**)

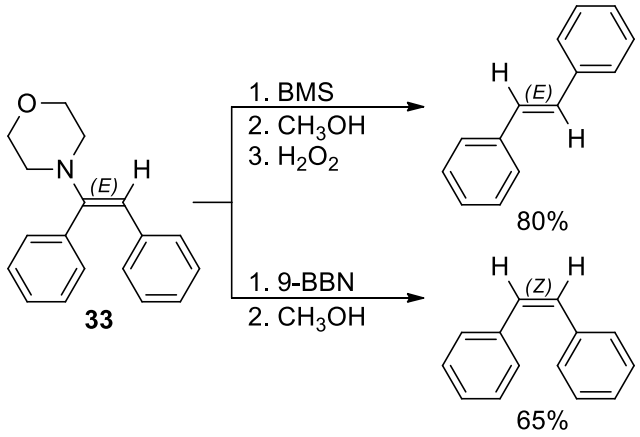
We then turned our attention to the reaction of 9-BBN with enamines derived from acyclic ketones. Thus, hydroboration of (*E*)-1-(4-morpholino)-1-phenyl-1-propene (**33**) with 9-BBN gave 1-phenyl-1-propene, which proved to be the pure (*Z*)-isomer in 80% isolated yield. We earlier showed that **33**, upon hydroboration with BMS followed by methanolysis and oxidation with basic hydrogen peroxide, gave pure *(E)*-1-phenyl-1-propene in 50% yield.[16] We found that sodium hydroxide alone did not induce this elimination reaction. We studied a series of oxidizing agents, and found that neutral hydrogen peroxide was the best reagent for carrying out this elimination. Thus, when the dimethyl boronate ester derived from **33** was treated with neutral hydrogen peroxide (*E*)-1-phenyl-1-propene was obtained in 75% isolated yield (Equation 29). This work demonstrated that we now had the ability to convert, by selecting the appropriate hydroboration procedure, a single acyclic ketone enamine into the corresponding (*E*)- or (*Z*)-alkene at will.



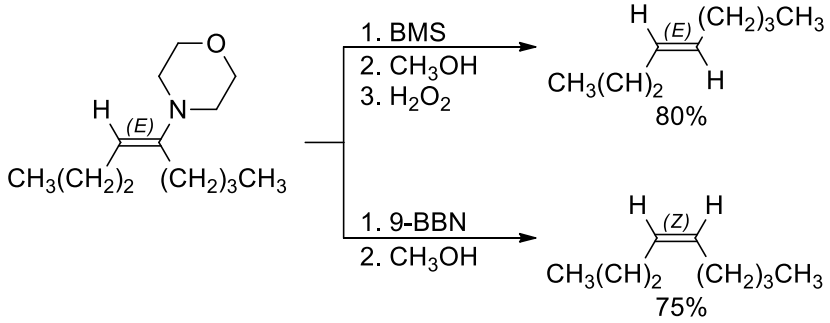

(**29**)

This methodology was further demonstrated with (*E*)-1,2-diphenyl-1-(4-morpholino)ethane (**37**, Equation 30) and (*E*)-5-(4-morpholino)-4-nonene (**38**, Equation 31).[19,20]

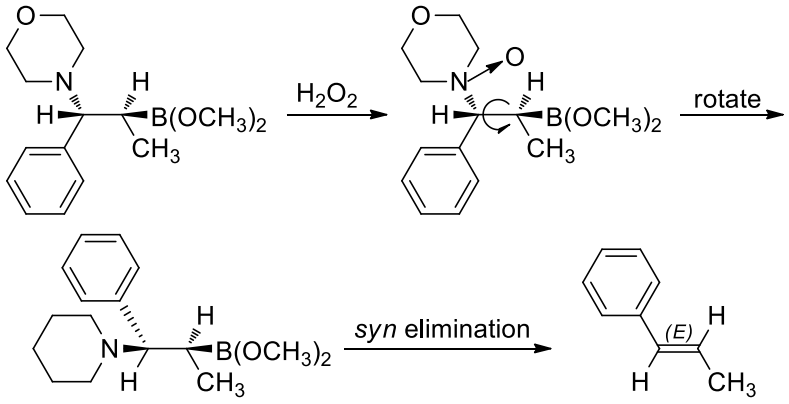



(**30**)



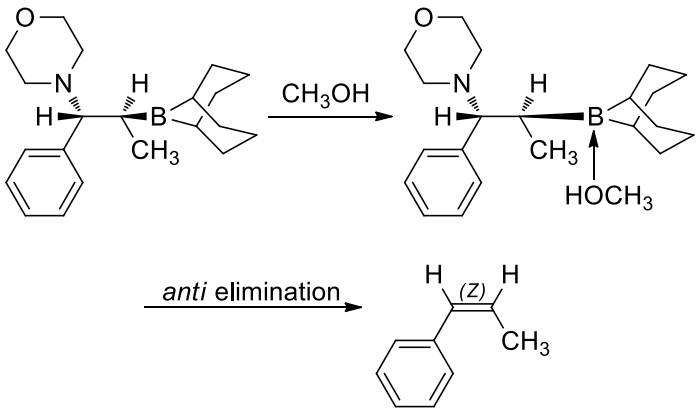

(**31**)

The mechanisms proposed to account for the stereochemical results obtained from acyclic ketone enamines are shown for (*E*)-1-(4-morpholino)-1-phenyl-1-propene (**33**, Equations 32 and 33).




(**32**)

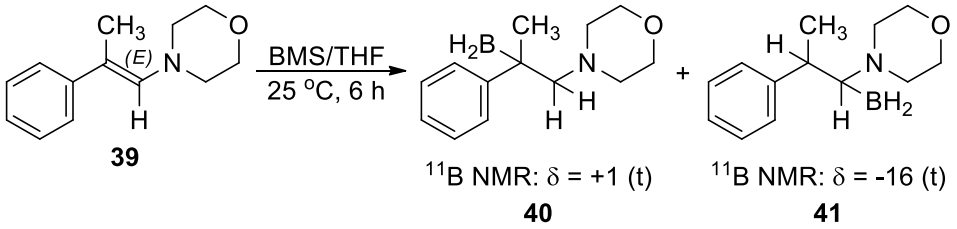
 




(**33**)

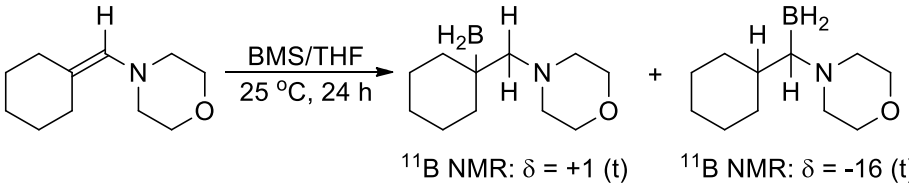
The study on the hydroboration of aldehyde enamines was next extended to β,β-disubstituted enamines.[22] We initially attempted the hydroboration of (*E*)-1-(4-morpholino)-2-phenyl-1-propene (**39**) with 9-BBN and, surprisingly, observed no reaction at 25 °C even after 24 hours.

When BMS in THF was used for the hydroboration of **39**, we obtained, at equilibrium, a 70:30 mixture of **40** and **41** (Equation 34).[22]




(**34**)

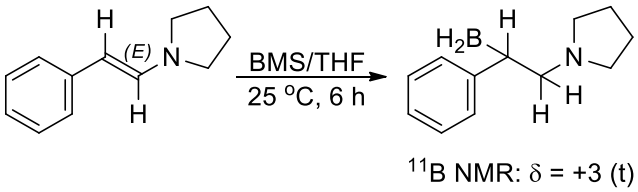
Similar results were obtained for the hydroboration of 4-(cyclohexylidenemethyl)morpholine (**42**) with BMS in THF (Equation 35).[22]



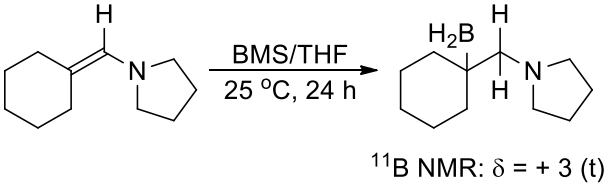

(**35**)

In contrast to the morpholino-enamines, hydroboration of the corresponding pyrrolidino-enamines with BMS in THF at 25 °C gave a single monoalkylborane product ( Equations 36 and 37).[2]

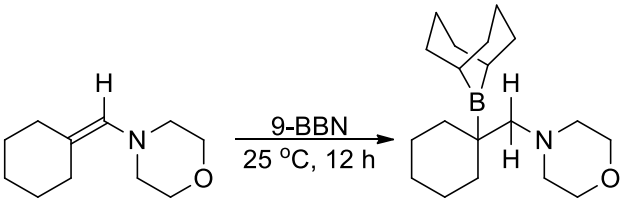



(**36**)

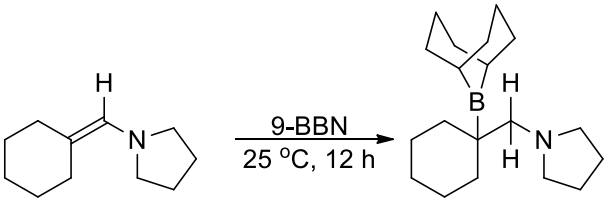



(**37**)

The hydroboration of aliphatic β,β-disubstituted enamines with 9-BBN was then investigated. Unlike **39**, these enamines were hydroborated at 25 °C within 12 hours and gave a single monoalkylborane product (Equations 38 and 39).[22]

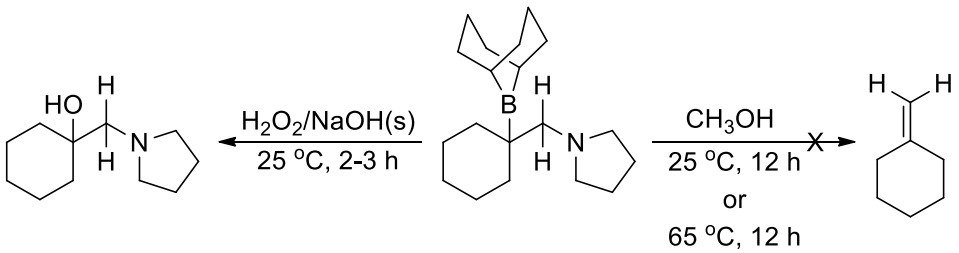



(**38**)




(**39**)

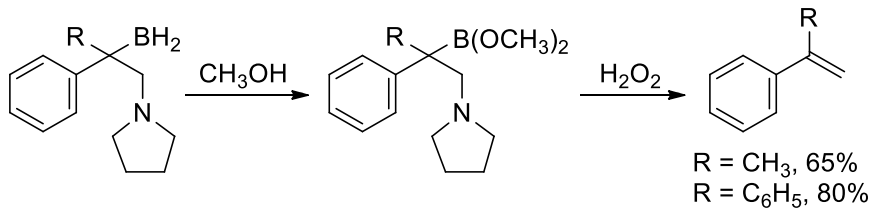
These trialkylboranes were stable toward methanol even at 65 °C, and were recovered unchanged (Equation 40). Fortunately, thermal decomposition of these trialkylboranes at 200 °C afforded the corresponding alkenes in moderate to excellent yields. Oxidation of these trialkylboranes using hydrogen peroxide and solid sodium hydroxide afforded the corresponding β-amino alcohols in good to excellent yields (Equation 40).[22]




(**40**)

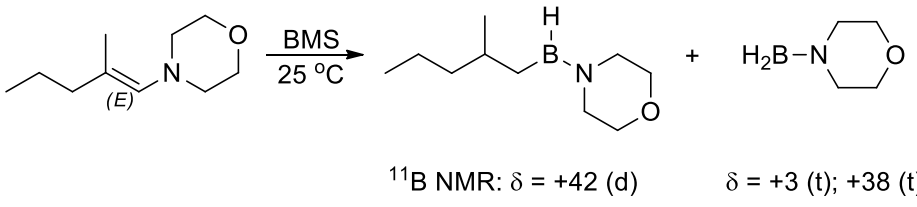
 

All of the monoalkylboranes obtained from β,β-disubstituted enamines and BMS reacted readily with methanol to form the corresponding dimethyl boronate esters. Only the dimethyl boronate esters obtained from phenyl-substituted β,β-disubstituted enamines underwent oxidative elimination with neutral hydrogen peroxide to afford the corresponding alkenes (Equation 41).[22]

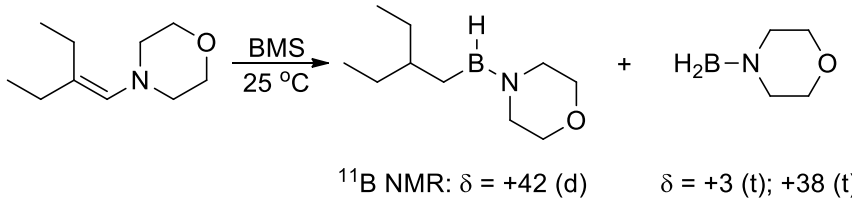



(**41**)

During our comprehensive investigation of the hydroboration of β,β-disubstituted enamines we observed the formation of β-aminoalkylboranes and aminoboranes as byproducts (Equations 42 and 43).[23]



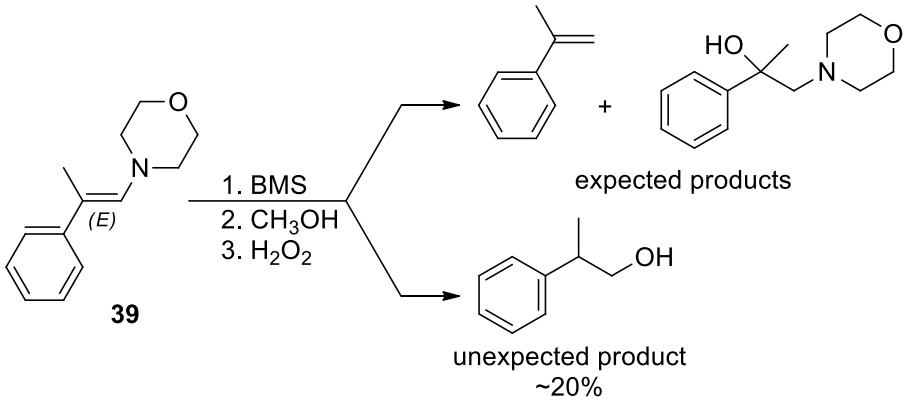

(**42**)




(**43**)

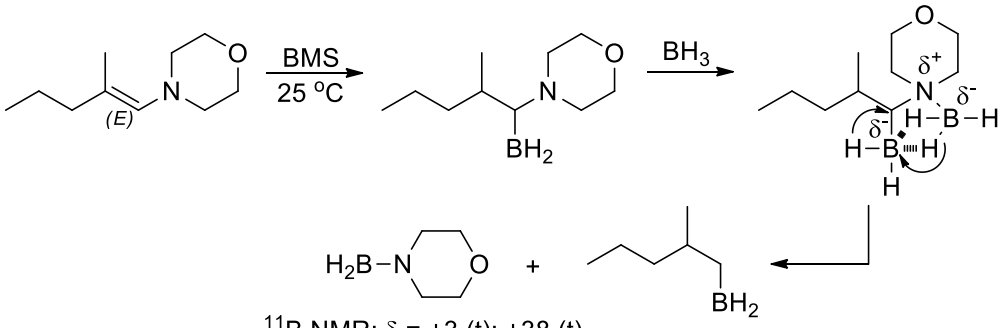
Additionally, during the hydroboration/oxidation of (*E*)-1-(4-morpholino)-2-phenyl-1-propene (**39**) we observed the formation of not only the expected alkene and amino alcohol but also an unexpected byproduct, 2-phenyl-1-propanol (Equation 44).[23]

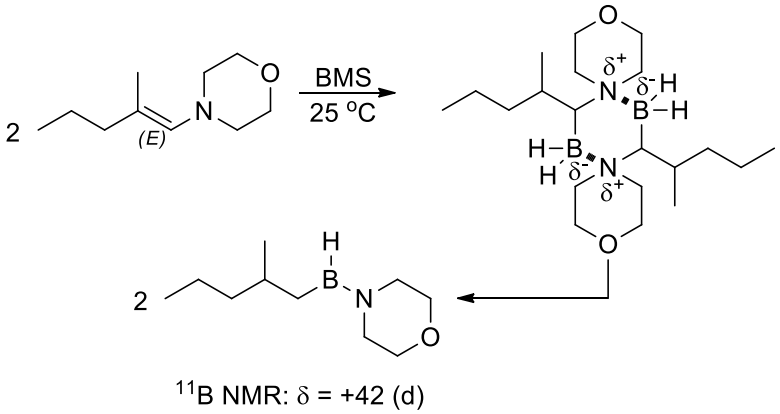



(**44**)

Two possible mechanisms were proposed to account for these observed products (Equations 45 and 46).[23] In the first mechanism (Equation 45), it was proposed that the α-aminoborane coordinates with borane, making the amine moiety a better leaving group. A hydride then migrates to displace the aminoborane product. In the second possible mechanism (Equation 46), the α-aminoborane was visualized to form a dimer, thereby making the amine moiety a better leaving group. Intramolecular hydride transfer then completes the rearrangement.[23] In both mechanisms the key step was the formation of a tetravalent boron atom and a positively charged nitrogen atom.




(**45**)




(**46**)

It was hypothesized that use of a stronger Lewis acid, such as $BF_3$, might facilitate the rearrangement reaction by forming a stronger adduct with the amino group. This proved to be the case. Hydroboration of β,β-disubstituted enamines with $BH_3$ in THF generated from sodium borohydride and boron trifluoride etherate afforded the rearranged products in significantly improved yield (Figure 2).[23]

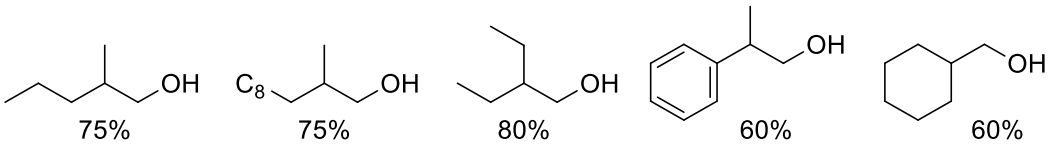
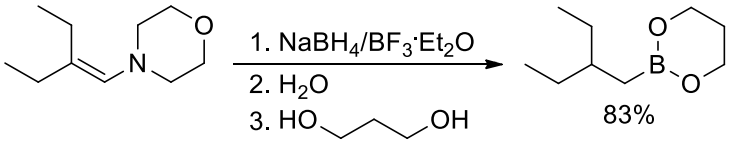
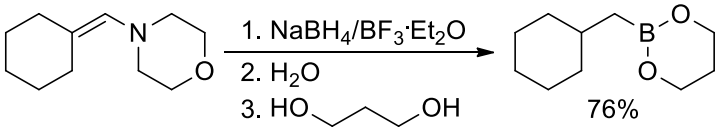



**Figure 2.** Alcohols obtained by oxidation (alkaline hydrogen peroxide) of the rearrangement of hydroborated ($NaBH_4/BF_3{\cdot}Et_2O$/THF) β,β-disubstituted aldehyde morpholino enamines (yields shown are of isolated and distilled products). $C_8 = CH_3(CH_2)_7$.

Non-oxidative workup of the rearrangement reaction mixture afforded the corresponding boronic acid derivatives in good yield (Equations 47 and 48).[23]

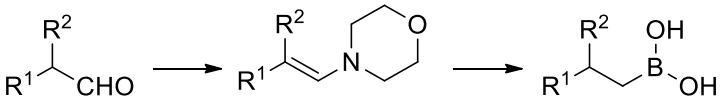



(**47**)




(**48**)

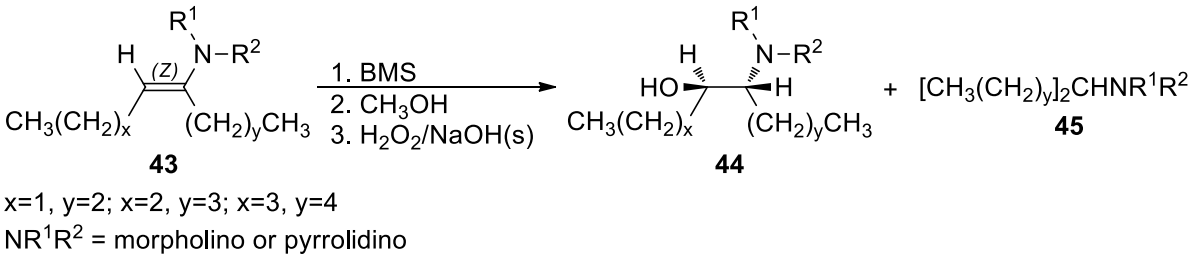
Thus, the hydroboration of a β,β-disubstituted aldehyde enamine followed by non-oxidative work-up with water provided a novel method of converting β-substituted aldehydes into the corresponding boronic acids (Equation 49).[23]




(**49**)

In preparation for examining the hydroboration of enamines with asymmetric hydroboration reagents, the hydroboration of two other classes of enamines with BMS was examined. The hydroboration of the enamines of symmetrical dialkyl ketones (**43**) with BMS followed by methanolysis and oxidation with basic hydrogen peroxide or trimethylamine *N*-oxide afforded the corresponding *threo*-β-amino alcohols (**44**) in moderate yields (Equation 50, Figure 3).[24] The crude amino alcohols were shown to contain small amounts (3-7%) of the corresponding reduction products (**45**).




(**50**)

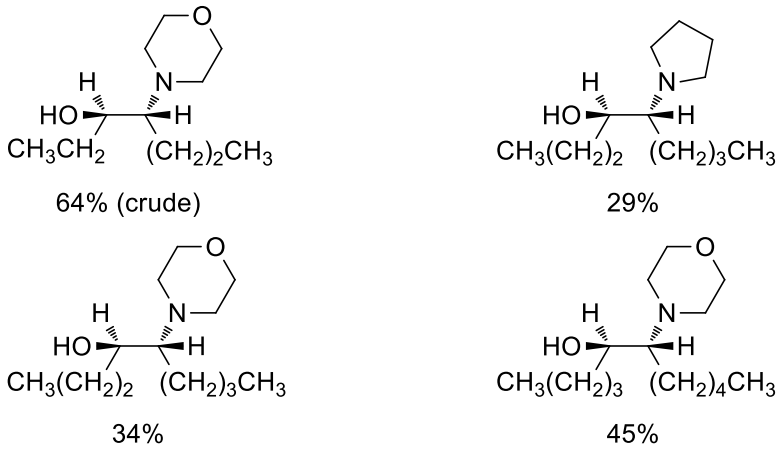
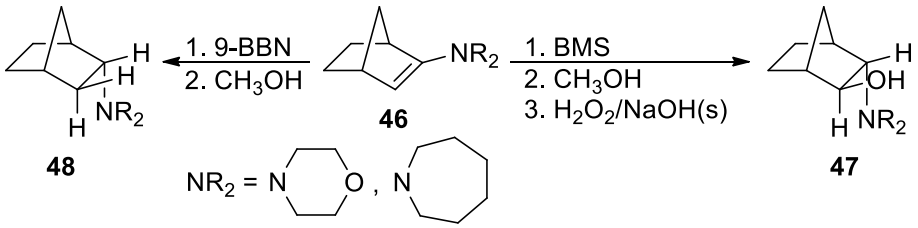



**Figure 3.** *threo*-β-Amino alcohols from enamines of symmetrical dialkyl ketones (yields shown are doe isolated and distilled products, except if otherwise specified).

Hydroboration of enamines (**46**) derived from 2-norbornanone, with BMS in THF followed by methanolysis and oxidation with basic hydrogen peroxide, afforded moderate yields of the corresponding *endo*-3-(dialkylamino)-*exo*-2-norbornanols (**47**).[25] Hydroboration of **46** with 9-BBN in THF followed by treatment with methanol afforded, instead of norbornene,[18,19,20] the corresponding *endo*-2-(dialkylamino)norbornanes (**48**, Equation 51).[25]



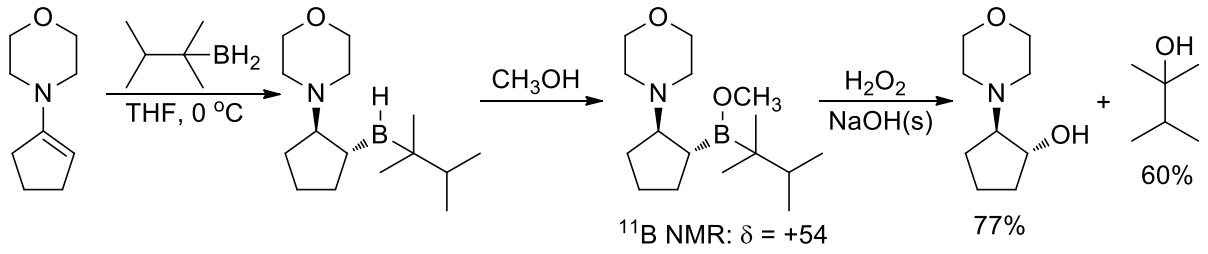

(**51**)

Nearly all of our previous studies on the hydroboration of enamines were conducted with BMS, an achiral hydroboration reagent. β-Mono-substituted and α,β- and β,β-disubstituted enamines were employed as the substrates. The resulting hydroboration adducts were then treated with methanol and the resulting boronate esters oxidized with alkaline hydrogen peroxide to give the corresponding β-amino alcohols in moderate to excellent yields.[16,20,22-24] The organoboranes derived from acyclic β-mono-substituted and α,β-disubstituted enamines,

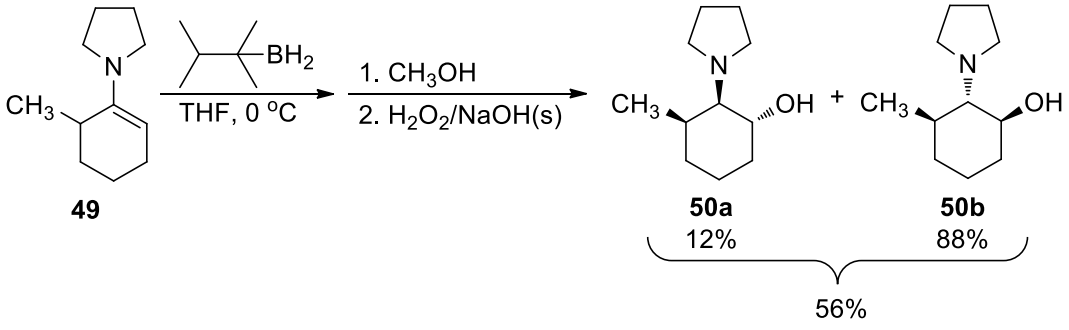
however, tended to undergo β-elimination.[16,20] Also, the trialkylboranes derived from enamines and 9-BBN underwent a methanol-promoted elimination to the corresponding alkene.[18,19,20] In order to better understand and suppress this elimination reaction, we conducted a study of the hydroboration of enamines with a variety of mono- and dialkylboranes.[26]

Hydroboration of 1-(4-morpholino)cyclopentene with thexylborane followed by methanolysis and oxidation with $H_2O_2$/NaOH afforded *trans*-2-(4-morpholino)cyclopentanol in 77% yield (Equation 52).[26]




(**52**)

Hydroboration/methanolysis/oxidation of the enamines derived from 2-methylcyclohexanone produced particularly interesting results. Borowitz[6] reported that hydroboration of the pyrrolidine enamine of 2-methylcyclohexanone (**49**) with $BH_3$·THF afforded a 64% yield of a 63:37 mixture of **50a** and **50b**. We repeated this reaction with BMS in THF and obtained a 55% yield of **50a** and **50b** in a ratio of 66:34. Surprisingly, hydroboration of **49** with thexylborane followed by methanolysis and oxidation afforded a 56% yield of a 12:88 mixture of **50a** and **50b**, essentially a total reversal of the results obtained with either $BH_3$·THF or BMS in THF (Equation 53).[26] These results are summarized in Table 1.



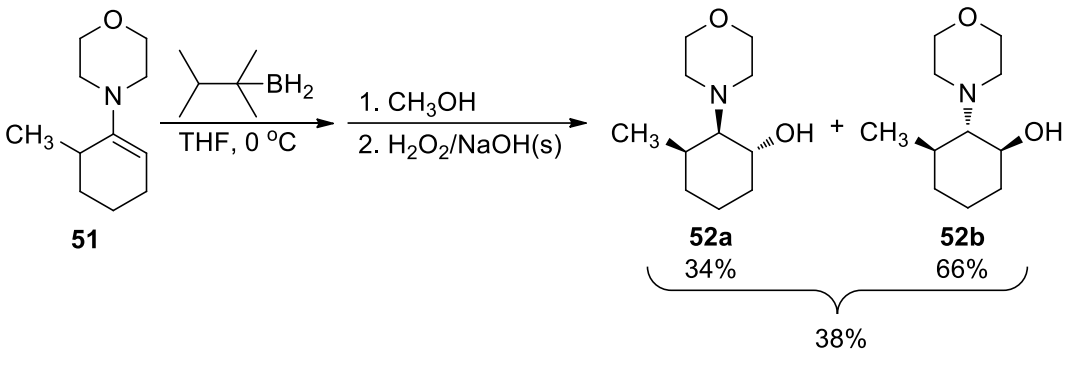

(**53**)

**Table 1.** Product ratios for the hydroboration/methanolysis/oxidation of the pyrrolidine enamine of 2-methylcyclohexanone (**49**)

| Hydroborating Agent | Isolated Yield, %(Ref.) | Ratio **50a**:**50b** |
|---|---|---|
| $H_3B$:THF, RT | 64(6) | 63:37 |
| BMS/THF, 0 °C | 55(26) | 66:34 |
| thexylborane/THF, 0 °C | 56(26) | 12:88 |

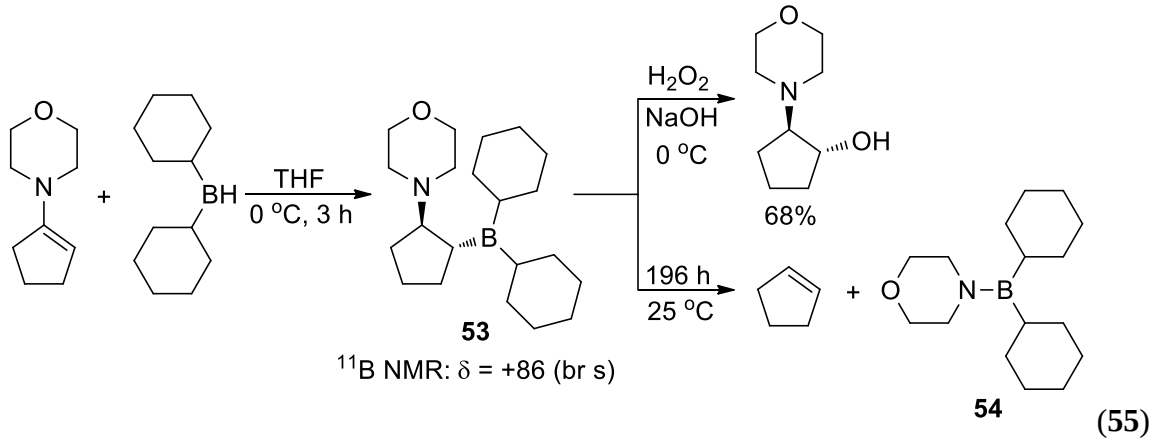
 

A similar result was obtained with the morpholine enamine of 2-methylcyclohexanone (**51)**, which afforded a 34:66 mixture of **52a** and **52b** (Equation 54).[26]




(**54**)

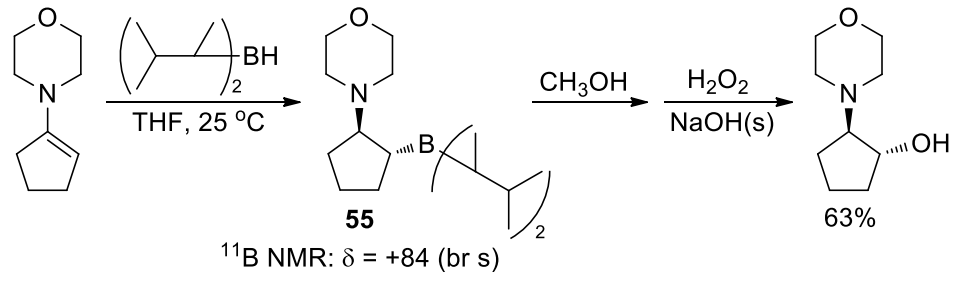
The hydroboration of 1-(4-morpholino)cyclopentene with dicyclohexylborane afforded a quantitative yield of the corresponding trialkylborane **53** (Equation 55).[26] When allowed to stand in THF at 25 °C for 196 hours, **53** slowly underwent elimination to give cyclopentene and β-(4-morpholino)dicyclohexylborane (**54**). Immediate oxidation of **53** with alkaline hydrogen peroxide, however, afforded a 68% yield of *trans*-2-(4-morpholino)cyclopentanol (Equation 55).[26]




(**55**)

The hydroboration of 1-(4-morpholino)cyclopentene with disiamylborane took two hours for completion of the reaction (Equation 56).[26] The resulting trialkylborane **55**, unlike those obtained with 9-BBN or dicyclohexylborane, was stable toward β-elimination at 25 °C. Oxidation of **55** with alkaline hydrogen peroxide afforded *trans*-2-(4-morpholino)cyclopentanol in 63% yield (Equation 56).[26]

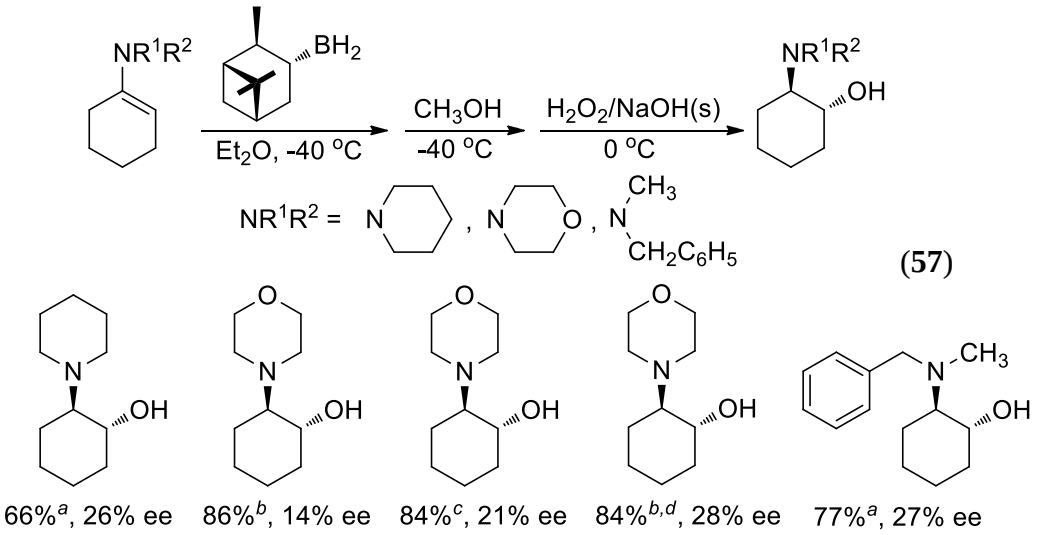
 




(**56**)

These results suggested that the β-elimination reaction is sensitive to the nature and steric requirements of the β-amino organoboranes.[26]

We then initiated a detailed investigation of the synthesis of chiral β-aminoalcohols using the asymmetric hydroboration reagents mono- and diisopinocampheylborane.[27] The initial asymmetric enamine hydroborations were carried out on a series of 1-(dialkyl-amino)cyclohexenes (Equation 57, Figure 4). The corresponding chiral β-aminoalcohols were obtained in moderate to excellent yields and modest enantiomeric excesses.[26,28]

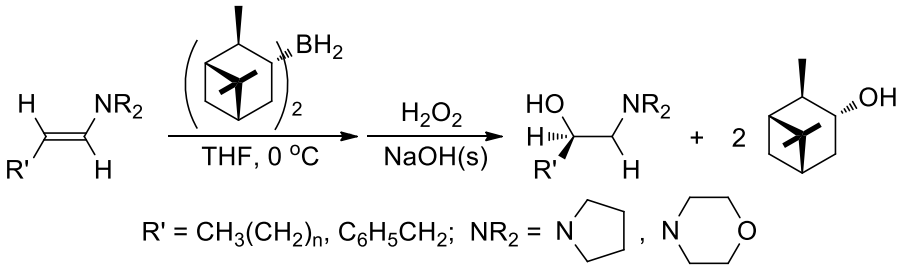



(**57**)

**Figure 4.** Synthesis of enantiomerically enriched β-aminoalcohols from 1-(dialkylamino)-cyclohexanones (isolated and distilled yields, % ee). [a] Hydroboration carried out at -40 °C. [b] Hydroboration carried out at 0 °C. [c] Hydroboration carried out at -30 °C. [d] Diisopinocampheylborane used as a complexing agent to retard the rate of hydroboration.

These results suggested that the more sterically demanding diisopinocampheylborane could give a highly enantiomeric hydroboration. This proved to be the case with acyclic aldehyde enamines, and oxidation of the of the intermediate trialkylboranes afforded the corresponding β-aminoalcohols in 52 to 85% yields and 50 to 86% ee (Equation 58, Figure 5).[26,28]




(**58**)

In general, the enantiomeric excesses of the pyrrolidine β-aminoalcohols were lower than those of the morpholine analogs (Figure 5). Separation of the enantiomeric β-aminoalcohols revealed that diisopinocampheylborane derived from the (+)-enantiomer of α-pinene afforded β-aminoalcohols enriched in the *R*-enantiomer.[26,28]

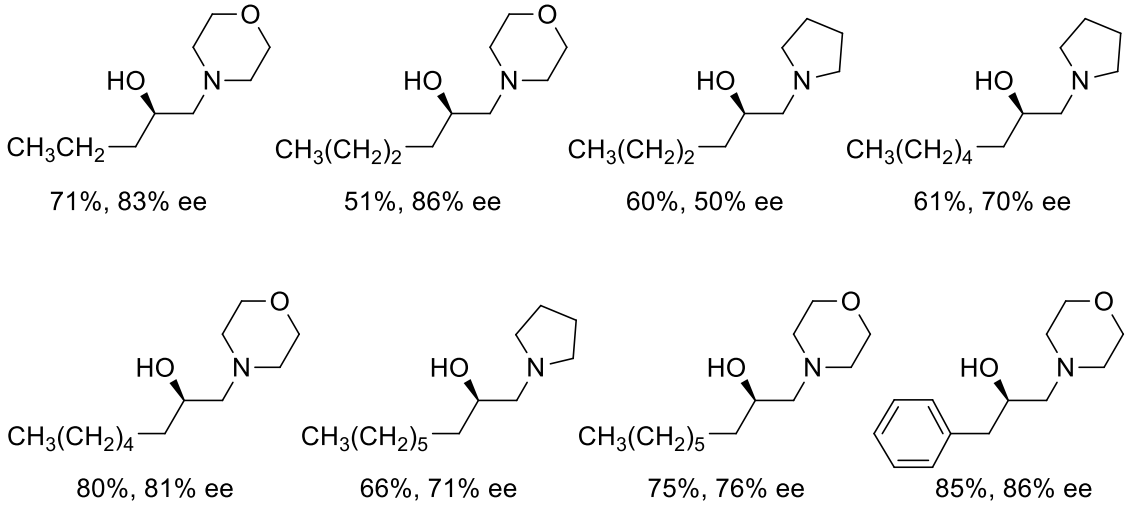
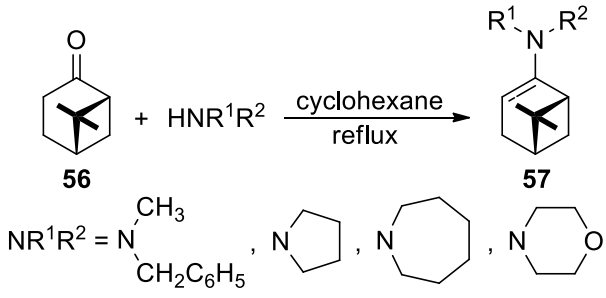



**Figure 5.** Asymmetric synthesis of β-amino alcohols from the corresponding aldehyde enamines (yields following isolation and distillation, % ee).

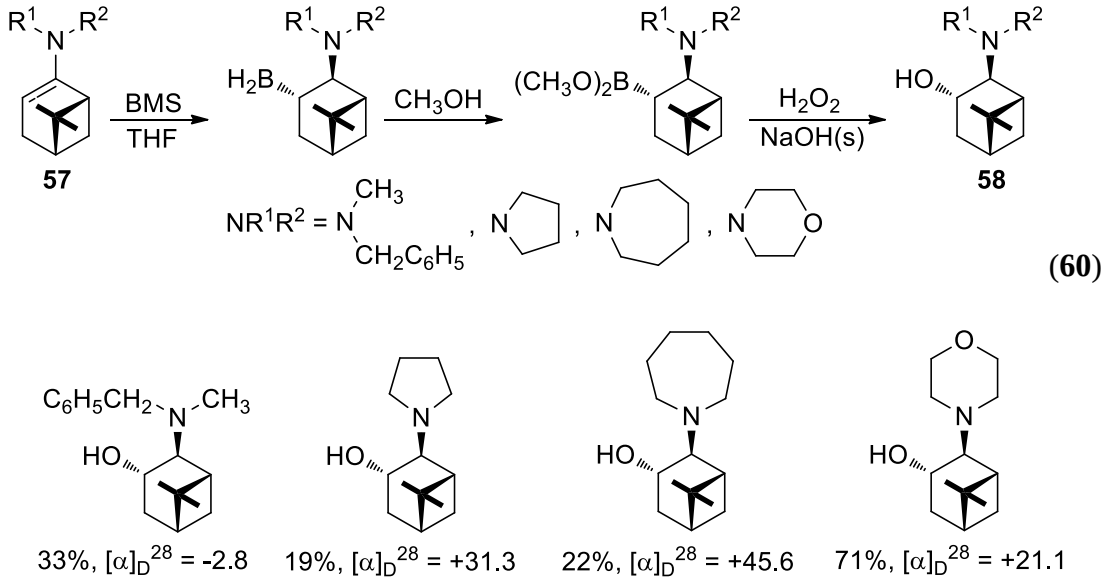
We next turned our attention to the hydroboration of enamines derived from a chiral ketone. The reaction of (1*R*,5*S*)-(+)-nopinone (**56**) with secondary amines in cyclohexane with the azeotropic removal of water afforded good to excellent yields of the corresponding enamines **57** (Equation 59).[29]




(**59**)

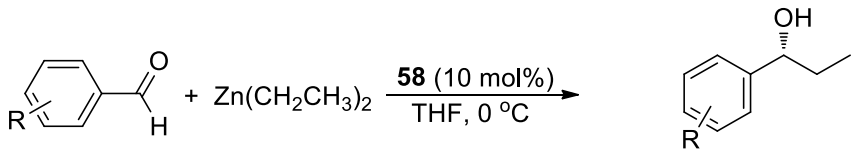
Hydroboration of the nopinone enamines **57** with BMS in THF followed by methanolysis and oxidation with basic hydrogen peroxide afforded the corresponding (1*R*,2*S*,3*S*,5*R*)-2-(dialkylamino)-6,6-dimethylbicyclo[3.1.1]heptan-3-ols (**58**) in moderate to good yields (Equation 60, Figure 6).[29]




(**60**)

**Figure 6.** (1*R*,2*S*,3*S*,5*R*)-2-(Dialkylamino)-6,6-dimethylbicyclo[3.1.1]heptan-3-ols from the hydroboration/methanolysis/oxidation of the corresponding enamines derived from (1*R*,5*S*)-(+)-nopinone (isolated, recrystallized yields, $[\alpha]_D^{28}$ c = 2.25, $CH_3OH$).

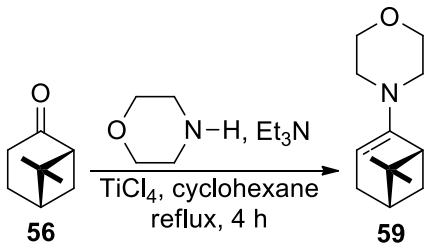
In spite of the fact that the hydroxyl group and the dialkylamino groups are *trans* to one another in the (1*R*,2*S*,3*S*,5*R*)-2-(dialkylamino)-6,6-dimethylbicyclo[3.1.1]heptan-3-ols (**58**), they proved to be effective catalysts for the addition of diethylzinc to aromatic aldehydes and afforded the corresponding (*R*)-(+)-1-aryl-1-propanols in 52 to 80% ee (Equation 61).[29]



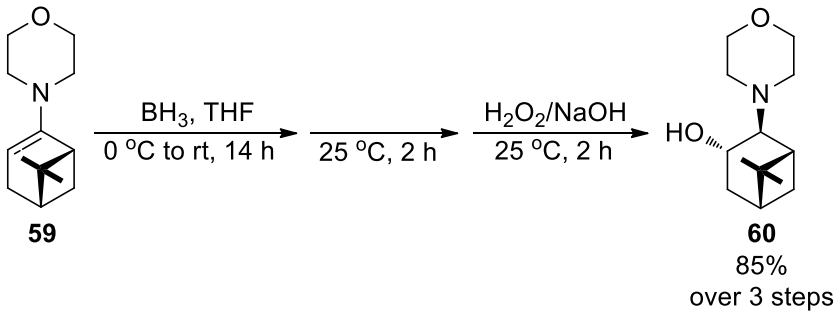

(**61**)

Very recently we reported[30] an improved synthesis of the morpholine enamine of (*R*)-(+)-nopinone (**56**), 4-[(1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl]morpholine (**59**, Equation 62). Also reported were improved conditions for the hydroboration/oxidation of **59** to give the corresponding β-amino alcohol, (1*R*,2*S*,3*S*,5*R*)-2-(4-morpholino)-6,6-dimethyl-bicyclo[3.1.1]-heptan-3-ol (**60**, Equation 63).[30]



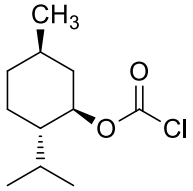

(**62**)




(**63**)

## 4. Analytical Methods for Determination of the ee of β-Amino Alcohols

In our early studies, the enantiomeric excess (ee) of the β-amino alcohols obtained by the asymmetric hydroboration of 1-(dialkylamino)cyclohexenes was determined by derivatizing the sample with (1*R*)-(-)-menthyl chloroformate (**61**) and analyzing the resulting mixture of diastereomers obtained by capillary gas chromatography (GC).[26,28]




**61**

In the course of our work on the asymmetric hydroboration of aldehyde enamines, Nicholson *et al*. developed an HPLC method for the separation of β-dialkylamino alcohols employing an amylose-based chiral stationary phase that gave excellent separation of the enantiomers without derivatization.[31-33]

## 5. References and Notes

1. Stork, G. reported before the Organic Chemistry Division at the 140th National Meeting of the American Chemical Society, Chicago, Ill., September 6, 1961. Since the hydroboration of

a double bond has been shown to be a *cis*-addition via a four-centered transition state (See: Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1959**, *81*, 247), the dialkylamino group and the hydroxyl group in **1** were presumed to be *trans* to one another.
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3. Lewis, J. W.; Pearce, A. A. *Tetrahedron Lett.* **1964**, *5*, 2039.
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